

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having at least one of
  - (a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;
  - 10 (b) a time to reach maximum concentration ( $T_{max}$ ) not greater than about 3 h after administration;
  - (c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;
  - (d) a terminal half-life ( $T_{1/2}$ ) not less than about 10 h; and
  - 15 (e) a maximum concentration ( $C_{max}$ ) not less than about 200 ng/ml.
2. The composition of Claim 1 having  $T_{max}$  not greater than about 3 h after administration.
3. The composition of Claim 1 having  $T_{max}$  not greater than about 1.7 h after administration.
- 20 4. The composition of Claim 1 having  $C_{max}$  not less than about 200 ng/ml.
5. The composition of Claim 1 having  $C_{max}$  not less than about 400 ng/ml.
6. The composition of Claim 1 wherein the amount of celecoxib in each dose unit is about 50 mg to about 800 mg.
7. The composition of Claim 1 wherein the amount of celecoxib in each dose unit is about about 75 mg to about 400 mg
- 25 8. The composition of Claim 1 wherein the amount of celecoxib in each dose unit is about 100 mg to about 200 mg.
9. A composition of Claim 1 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for providing therapeutically or

prophylactically effective inhibition of cyclooxygenase-2.

10. A composition of Claim 1 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for treatment or prophylaxis of a cyclooxygenase-2 mediated condition or disorder.
- 5 11. The composition of Claim 1 wherein said dose units are in a form of discrete solid articles.
12. The composition of Claim 11 wherein said articles are tablets, pills, hard or soft capsules, lozenges, sachets or pastilles.
13. A composition of Claim 11 in the form of unit dosage capsules or tablets.
- 10 14. The composition of Claim 13 wherein said excipient(s) are selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents and lubricants.
15. The composition of Claim 13 wherein said excipient(s) include one or more pharmaceutically acceptable diluents in a total amount of about 5% to about  
15 99% by weight of the composition.
16. The composition of Claim 15 wherein said diluents are selected from the group consisting of lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, Celutab, inositol, hydrolyzed  
20 cereal solids, amylose, Rexcel, powdered cellulose, calcium carbonate, glycine and bentonite.
17. The composition of Claim 15 wherein said diluents are selected from the group consisting of lactose and microcrystalline cellulose.
- 25 18. The composition of Claim 15 wherein said diluents comprise lactose.
19. The composition of Claim 13 wherein said excipients include one or more pharmaceutically acceptable disintegrants in a total amount of about 0.2% to about 30% by weight of the composition.
20. The composition of Claim 19 wherein said disintegrants are selected from the

group consisting of starches, sodium starch glycolate, clays, celluloses, alginates, pregelatinized corn starches, crospovidone and gums.

21. The composition of Claim 19 wherein said disintegrants comprise croscarmellose sodium.
- 5 22. The composition of Claim 13 wherein said excipients include one or more pharmaceutically acceptable binding agents in a total amount of about 0.5% to about 25% by weight of the composition.
- 10 23. The composition of Claim 22 wherein said binding agents are selected from the group consisting of acacia, tragacanth, sucrose, gelatin, glucose, starch, celluloses, methylcellulose, sodium carboxymethylcellulose, alginic acid and salts thereof, magnesium aluminum silicate, polyethylene glycols, guar gum, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose and pregelatinized starch.
- 15 24. The composition of Claim 22 wherein said binding agents comprise polyvinylpyrrolidone.
25. The composition of Claim 13 wherein said excipients include one or more pharmaceutically acceptable wetting agents in a total amount of about 0.25% to about 15% by weight of the composition.
- 20 26. The composition of Claim 25 wherein said wetting agents comprise an anionic surfactant.
27. The composition of Claim 25 wherein said wetting agents comprise sodium lauryl sulfate.
- 25 28. The composition of Claim 13 wherein said excipients include one or more pharmaceutically acceptable lubricants in a total amount of about 0.1% to about 10% by weight of the composition.
29. The composition of Claim 28 wherein said lubricants are selected from the group consisting of glyceryl behapate, stearates, stearic acid, hydrogenated vegetable oils, talc, waxes, Stearowet, boric acid, sodium benzoate, sodium

acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, sodium lauryl sulfate and magnesium lauryl sulfate.

30. The composition of Claim 28 wherein said lubricants comprise magnesium stearate.
- 5 31. A composition of Claim 13 comprising
- (a) one or more pharmaceutically acceptable diluents in a total amount of about 10% to about 85% by weight of the composition;
  - (b) one or more pharmaceutically acceptable disintegrants in a total amount of about 0.2% to about 10% by weight of the composition; and
  - 10 (c) one or more pharmaceutically acceptable binding agents in an amount of about 0.5% to about 10% by weight of the composition.
32. A composition of Claim 31 further comprising
- (d) one or more pharmaceutically acceptable wetting agents in a total amount of about 0.4% to about 10% by weight of the composition;
  - 15 and/or
  - (e) one or more pharmaceutically acceptable lubricants in a total amount of about 0.2% to about 8% by weight of the composition.
33. The composition of Claim 31 wherein said diluent(s) comprise lactose.
34. The composition of Claim 31 wherein said disintegrant(s) comprise
- 20 croscarmellose sodium.
35. The composition of Claim 31 wherein said binding agent(s) comprise polyvinylpyrrolidone.
36. The composition of Claim 32 wherein said wetting agent(s) comprise sodium lauryl sulfate.
- 25 37. The composition of Claim 32 wherein said lubricants comprise magnesium stearate.
38. The composition of Claim 13 wherein celecoxib is present in an amount of about 1% to about 95% by weight of the composition.
39. The composition of Claim 13 wherein celecoxib is present in an amount of

about 25% to about 85% by weight of the composition.

40. A composition of Claim 13 comprising
- (a) about 1 to about 95 weight percent of celecoxib;
  - (b) about 5 to about 99 weight percent of lactose;
  - 5 (c) about 2 to about 10 weight percent of croscarmellose sodium;
  - (d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone;
  - (e) 0 to about 7 weight percent of sodium lauryl sulfate; and
  - (f) 0 to about 5 weight percent of magnesium stearate.
41. A composition of Claim 13 comprising
- 10 (a) about 25 to about 85 weight percent of celecoxib;
  - (b) about 5 to about 70 weight percent of lactose;
  - (c) about 0.2 to about 6 weight percent of croscarmellose sodium;
  - (d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone;
  - (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and
  - 15 (f) about 0.2 to about 8 weight percent of magnesium stearate.
42. A composition of Claim 13 comprising, in each dose unit,
- (a) about 80 to about 220 mg of celecoxib;
  - (b) about 30 to about 225 mg of lactose;
  - (c) about 0.5 to about 25 mg of croscarmellose sodium;
  - 20 (d) about 0.5 to about 25 mg of polyvinylpyrrolidone;
  - (e) 0 to about 70 mg of microcrystalline cellulose;
  - (f) 0 to about 25 mg of sodium lauryl sulfate; and
  - (g) 0 to about 10 mg of magnesium stearate.
43. A composition of Claim 13 comprising unit dosage capsules each containing
- 25 (a) about 100 mg of celecoxib;
  - (b) about 149.75 mg of lactose monohydrate;
  - (c) about 2.7 mg of croscarmellose sodium;
  - (d) about 6.75 mg of polyvinylpyrrolidone;
  - (e) about 8.1 mg of sodium lauryl sulfate; and
  - 30 (f) about 2.7 mg of magnesium stearate.

44. A composition of Claim 13 comprising unit dosage capsules each containing
- (a) about 200 mg of celecoxib;
  - (b) about 49.75 mg of lactose monohydrate;
  - (c) about 2.7 mg of croscarmellose sodium;
  - 5 (d) about 6.75 mg of polyvinylpyrrolidone;
  - (e) about 8.1 mg of sodium lauryl sulfate; and
  - (f) about 2.7 mg of magnesium stearate.
45. A composition of Claim 13 comprising unit dosage tablets each containing
- (a) about 100 mg of celecoxib;
  - 10 (b) about 101.88 mg of lactose monohydrate;
  - (c) about 7.5 mg of croscarmellose sodium;
  - (d) about 6.25 mg of polyvinylpyrrolidone;
  - (e) about 25 mg of microcrystalline cellulose;
  - (f) about 7.5 mg of sodium lauryl sulfate; and
  - 15 (g) about 1.88 mg of magnesium stearate.
46. A composition of Claim 13 comprising unit dosage tablets each containing
- (a) about 200 mg of celecoxib;
  - (b) about 203.8 mg of lactose monohydrate;
  - (c) about 15 mg of croscarmellose sodium;
  - 20 (d) about 12.5 mg of polyvinylpyrrolidone;
  - (e) about 50 mg of microcrystalline cellulose;
  - (f) about 15 mg of sodium lauryl sulfate; and
  - (g) about 3.75 mg of magnesium stearate.
47. A composition of Claim 13 comprising unit dosage capsules or tablets each
- 25 providing a 100 mg or 200 mg dose of celecoxib.
48. A composition of Claim 13 prepared by a process wherein the celecoxib, together with one or more excipients, is directly encapsulated or directly compressed into tablets.
49. A composition of Claim 13 prepared by a process wherein the celecoxib, together with one or more excipients, is wet granulated prior to encapsulation
- 30 or compression into tablets.

50. A composition of Claim 13 prepared by a process wherein the celecoxib, together with one or more excipients, is dry granulated prior to encapsulation or compression into tablets.
51. A composition of Claim 1 that is a substantially homogeneous flowable mass from which single dose units are measurably removable.
52. The composition of Claim 51 wherein said flowable mass is a particulate or granular solid.
53. The composition of Claim 51 wherein said flowable mass is a suspension having the celecoxib in a solid particulate phase dispersed in an aqueous phase.
54. The composition of Claim 53 wherein said excipient(s) include a pharmaceutically acceptable wetting agent.
55. The composition of Claim 54 wherein said wetting agent is polysorbate 80.
56. A composition of Claim 53 further comprising a solvent from which the celecoxib is precipitated to prepare the suspension.
57. The composition of Claim 56 wherein said solvent is ethanol.
58. The composition of Claim 53 wherein the aqueous phase comprises a palatable vehicle selected from the group consisting of water, syrup and fruit juice.
59. The composition of Claim 58 wherein said vehicle is apple juice.
60. A composition of Claim 1 providing, upon oral ingestion, a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 h after ingestion.
61. The composition of Claim 60 wherein said therapeutic effect is provided over an interval of about 24 h after ingestion.
62. The composition of Claim 1 wherein, upon oral ingestion, at least about 50% of the celecoxib is released, as determined *in vitro*, within about 15 minutes after ingestion.
63. A composition of Claim 1 further comprising one or more opioid or analgesic

drugs.

64. A composition of Claim 63 wherein said opioid or analgesic drugs are selected from the group consisting of narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers.
65. A composition of Claim 63 wherein said opioid or analgesic drugs are selected from the group consisting of morphine, meperidine, codeine, pentacozine, buprenorphine, butorphanol, dexocine, meptazinol, hydrocodone, oxycodone, methadone, DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetaminophen, propoxyphene, nalbuphene, E-4018, filenadol, mirfentanil, amitriptyline, DuP 631, GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate and isolated (+) and (-) enantiomers, AXC-3742, SNX-111, ADL2-1294, CT-3 and CP-99994.
66. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having relative bioavailability not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution containing an equivalent amount of celecoxib.
67. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a distribution of celecoxib particle sizes such that  $D_{90}$  of the particles is less than 200  $\mu\text{m}$ , in the longest dimension of said particles.
68. The composition of Claim 67 wherein  $D_{90}$  of the particles is less than 100  $\mu\text{m}$ , in the longest dimension of said particles.
69. The composition of Claim 67 wherein  $D_{90}$  of the particles is less than 40  $\mu\text{m}$ , in the longest dimension of said particles.



70. The composition of Claim 67 wherein  $D_{90}$  of the particles is less than 25  $\mu\text{m}$ , in the longest dimension of said particles.
71. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a mean celecoxib particle size of about 1  $\mu\text{m}$  to about 10  $\mu\text{m}$ .
72. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of Claim 1 once or twice a day.
73. The method of Claim 72 wherein the condition or disorder is rheumatoid arthritis.
74. The method of Claim 72 wherein the condition or disorder is osteoarthritis.
75. The method of Claim 72 wherein the condition or disorder, or a symptom of the condition or disorder, is pain.
76. A method of preparing a composition of Claim 13 comprising
- (a) wet granulating celecoxib together with one or more excipients to form a wet granulated mixture;
  - (b) drying the wet granulated mixture; and
  - (c) encapsulating the dried granulated mixture or compressing the dried granular mixture into tablets.
77. The method of Claim 76 wherein, prior to the wet granulating step, the celecoxib is milled such that  $D_{90}$  of the resulting particles is less than 200  $\mu\text{m}$ , in the longest dimension of said particles.
78. The method of Claim 76 wherein, prior to the wet granulating step, the celecoxib is milled such that  $D_{90}$  of the resulting particles is less than 100  $\mu\text{m}$ , in the longest dimension of said particles.
79. The method of Claim 76 wherein, prior to the wet granulating step, the celecoxib is milled such that  $D_{90}$  of the resulting particles is less than 40  $\mu\text{m}$ .

in the longest dimension of said particles.

80. The method of Claim 76 wherein, prior to the wet granulating step, the celecoxib is milled such that  $D_{90}$  of the resulting particles is less than 25  $\mu\text{m}$ ,  
in the longest dimension of said particles.
- 5 81. The method of Claim 80 wherein said milling is performed with a pin mill.
82. The method of Claim 81 wherein said milling results in a mean celecoxib  
particle size of about 1  $\mu\text{m}$  to about 10  $\mu\text{m}$ .
83. The method of Claim 81 wherein said milling results in a mean celecoxib  
particle size of about 5  $\mu\text{m}$  to about 7  $\mu\text{m}$ .